REMARKS

Introduction

Receipt of a non-final office action dated October 19, 2007 is acknowledged. In the action, the claims are rejected allegedly for failing to meet the written description requirement (claims 64-65), non-enablement (claims 55-56, 58 and 60-80), indefiniteness (claims 55-56, 58 and 60-80), lack of novelty in view of US Patent No. 5,210,075 ("'075 patent") (claims 55, 56 and 68), US Patent No. 5,888,510 ("'510 patent") (claim 58), Nishimoto *et al.* (claim 58), EP 1074268 (claim 58), WO 97/10338 (claims 55-56), WO 99/64070 (claims 55-56), and Choy *et al.* (claims 55-56, 58, 60-61 and 68), and obviousness reasons over Choy *et al.* (claims 55-56, 58, 60, 61, 62-63, 68-80) and Choy *et al.* in view of US Patent No. 5,530,101 ("'101 patent") (claims 55-56, 58, 60, 61-63, 66 and 68-80).

Status of the Claims

In this response, applicants amended claims 55, 56, 58, 68, 69, 73, 76, 79 and 80, cancelled claims 60, 72 and 75, and added new claims 81-83. Support for the amended and new claims can be found throughout the specification, Example 1, and on pages 4-6 and 10 in particular. Upon entry of this amendment, claims 55, 56, 58, 61-71, 73, 74, and 76-83 will be under examination.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

It is acknowledged that the foregoing amendments are submitted after final rejection. However, because the amendments do not introduce new matter or raise new issues, and because the amendments either place the application in condition for allowance or at least in better condition for appeal, entry thereof by the Examiner is respectfully requested.

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Rejection of the Claims Under 35 U.S.C. § 112, 1st Paragraph

Claims 64 and 65 are rejected under 35 U.S.C. § 112 as allegedly failing to meet the written description requirement. In particular, the Office rejects the claims because "[t]he reproduction of antibodies from the disclosed hybridoma is an extremely unpredictable event" and the hybridoma with accession number FERM BP-2998 . . . must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public." Office action at 2. Applicants respectfully traverse this ground for rejection.

A hybridoma cell line producing PM-1 has been deposited as FERM BP-2998, and a hybridoma cell line producing MR16-1 has been deposited as FERM BP-5875, both as international depositions under the Budapest Treaty, as described on page 10, lines 21-31 of the originally filed application. Accordingly, the antibodies of the present invention are available. Please see accompanying declaration in Exhibit A, attached hereto.

Claims 55-56, 58 and 60-80 are rejected under 35 U.S.C. § 112 as allegedly not enabled. Specifically, the claims are rejected because the specification is enabling for a method for treating rheumatoid arthritis comprising administering an IL-6 receptor antibody and an immunosuppressant, wherein the antibody is a PM-1 or MR16-1 or a humanized antibody to a human IL-6 receptor, MRA, but not "a method for treating an IL-6 related disease, comprising administering an IL-6 antagonist and an immunosuppressant to a patient requiring such treatment or a method for the effect enhancement on the use of an IL-6 antagonist for the treatment of IL-6 related disease, comprising administering immunosuppressants and an IL-6 antagonist to a patient requiring such treatment. Office action at 4.

In the interest of expediting prosecution, and without acquiescing to the Office's rejection, applicants amended the claims to refer to an anti-IL-6 receptor antibody which inhibits binding of IL-6 to the IL-6 receptor by binding to the IL-6 receptor to block signaling of IL-6 biological activity into cells instead of an IL-6 antagonist. Support for this amendment can be found on page 10, lines 11-13 of the originally filed application. Accordingly, suitable antibodies for use in the present invention operate by this mechanism

and ultimately result in inhibition of IL-6 biological activity. Exemplary antibodies include PM-1, MR16-1 and MRA, but one of skill in the art would know how to make and use other anti-IL-6 receptor antibodies that inhibit biological activity by binding to the IL-6 receptor.

Additionally, applicants amended the claims to refer to treating rheumatoid arthritis. Applicants trust that these amendments address the Office's concerns.

Rejection of the Claims Under 35 U.S.C. § 112, 2nd Paragraph

Claims 55-56, 58 and 60-80 are rejected as allegedly indefinite. Specifically, the claims are rejected for their recitation of "an IL-6 related disease" and "IL-6 antagonist." In the interest of expediting prosecution, and without acquiescing to the Office's rejection, applicants amended the claims to recite a specific group of IL-6 related diseases and an anti-IL-6 receptor antibody. Applicants trust these amendments address the Office's concerns.

Rejection of the Claims Under 35 U.S.C. § 102

Claims 55, 56 and 68 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by the '075 patent. Applicants respectfully disagree.

The '075 patent does not describe treating an IL-6 mediated disease with an anti-IL-6 receptor antibody as recited in the claims. In fact, the '075 patent only states administration with an IL-6 antagonist peptide and does not enable treatment with an anti- IL-6R antibody. In addition, the '075 patent does not describe treatment with a specific immunosuppressant substance such as MTX. Accordingly, the '075 patent does not anticipate the present invention.

Claim 58 is rejected as allegedly anticipated by the '510 patent, Nishimoto *et al.*, or EP 1074268. Applicants respectfully disagree.

Claim 58 recites a limitation on the dosage and time interval of administration, *i.e.*, 4 mg/kg/4 weeks or more. Neither the '510 patent, the Nishimoto reference nor EP 107268 describe the claimed administration amount and the administration interval of the present invention. Accordingly, claim 58 is not anticipated by the cited art.

Claims 55 and 56 are rejected as anticipated by WO 99/64070, Choy *et al.*, or WO 97/10338, and claims 58, 60-61 and 68 as anticipated by Choy only. Applicants respectfully disagree.

Applicants respectfully assert that neither WO 99/64070, Choy *et al.*, nor WO 97/10338 described the combined use of an anti-IL-6 receptor antibody and MTX, or the dosage 4 mg/kg/4 weeks or more, as recited in the claims. Accordingly, these references do not destroy novelty of the presently claimed invention.

Rejection of the Claims Under 35 U.S.C. § 103

Claims 55-56, 58, 60-63 and 68-80 are rejected as allegedly obvious over Choy. In particular, the claims are rejected because the reference "teaches a method of treatment of rheumatoid arthritis by using an anti-IL-6 receptor antibody (MRA) . . ." and "the patients were allowed to take prednisolone . . . ." Office action at 11. Thus, the Office concludes that it would be obvious for one of skill in the art to substitute and administer the immunosuppressant MTX in the method disclosed by Choy and the motivation to do so would be because Choy teaches that concomitant oral steroid treatment of prednisolone was permitted.

These same claims were also rejected as allegedly obvious over Choy, in view of Queen, the '101 patent, for these same reasons, in addition to the argument that it would have been obvious for one of skill in the art to obtain humanized antibodies as taught by Queen to an IL-6R protein as taught by Choy. Office action at 12-13. Applicants respectfully disagree.

Applicants respectfully assert that Choy describes a combined use of an anti-IL-6 receptor antibody and prednisolone, and there would be no reasonable expectation of success to replace prednisolone with immunosuppressants. Moreover, the Choy reference does not motivate a person with ordinary skill in the art to replace prednisolone with immunosuppressants for the following reasons.

(1) The Choy reference refers to "Concomitant oral steroid treatment was permitted if the dose was ... ." The phrase "was permitted" means that Choy did not positively use

prednisolone. A person with ordinary skill in the art who reads the above description may consider that administration of prednisolone does not provide a substantial effect and therefore, only stated that steroid use was permitted, and not required or even urged. In fact, only one part of Choy refers to prednisolone, and the remainder of the reference, such as the Results and Discussion sections do not refer to prednisolone per se or the combined use of prednisolone.

(2) The presently claimed invention is directed to a combined use of an anti-IL-6 receptor antibody and MTX, which is an immunosuppressant. On the other hand, Choy on page 3144, lower right column, beginning at line 11 describes the use of parenteral and/or intraarticular steroids, immunosuppressants, investigational drugs and oral anticoagulant drugs, and specifically states that such drugs within 4 weeks before administration of the study medication was not permitted. Accordingly, Choy explicitly and intentionally prohibited the use of immunosuppressants within a give time frame. Therefore, not only does Choy not motivate the use of immunosuppressants in combination with an anti-IL-6R antibody, the reference also teaches away from the combined use.

(3) Choy does not suggest that combined use of an anti-IL-6 receptor antibody provides a better therapeutic effect in comparison with the use of an anti-IL-6 receptor antibody alone. Thus, a person of ordinary skill in the art would be lead to believe, from the teachings of Choy, that the prednisolone does not provide a substantial effect. This, however, is in contrast to the present invention which demonstrates that a combined use of an anti-IL-6 receptor antibody and MTX provides a better therapeutic effect in comparison with a single use of an anti-IL-6 receptor antibody. See Example 1 of the present application. Such an advantage was unexpected and not predicted from the teachings of Choy alone, or in combination with the '101 patent.

Therefore, for at least these reasons, applicants respectfully request the rejections be withdrawn.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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By _____

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